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U.S. PATENT APPLICATION

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Invention: IONTOPHORETIC DRUG DELIVERY ELECTRODES AND METHOD

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SPECIFICATION

BACKGROUND OF THE INVENTION

1. Field of the Invention:

This invention relates generally to the transdermal electrokinetic mass transfer of medication into a diseased tissue, and, more specifically, to a medicament containing iontophoresis electrode for the delivery of medication across the skin and into diseased tissues and blood vessels adjacent to the delivery site.

2. Prior Art:

Iontophoresis has been employed for several centuries as a means for applying medication locally through a patient's skin and for delivering medicaments to the eyes and ears. The application of an electric field to the skin is known to greatly enhance the skin's permeability to various ionic agents. This permeability change has been used, for example, to enhance transcutaneous transport of glucose for monitoring blood glucose levels. The use of iontophoretic transdermal delivery techniques has obviated the need for hypodermic injection for many medicaments, thereby eliminating the concomitant problems of trauma, pain and risk of infection to the patient.

Iontophoresis involves the application of an electromotive force to drive or repel oppositely charged ions through the dermal layers into a target tissue. Particularly suitable target tissue include tissues adjacent to the delivery site for localized treatment or tissues remote therefrom in which case the medicament enters into the circulatory system and is transported to a tissue by the blood. Positively charged ions are driven into the skin at an anode while negatively charged ions are driven into the skin at a cathode. Studies have shown increased skin penetration of drugs at anodic or cathodic electrodes regardless of the predominant molecular ionic charge on

the drug. This effect is mediated by polarization and osmotic effects.

Regardless of the charge of the medicament to be administered, a iontophoretic delivery device employs two electrodes (an anode and a cathode) in conjunction with the patient's skin to form a closed circuit between one of the electrodes (referred to herein alternatively as a "working" or "application" or "applicator" electrode) which is positioned at the delivered site of drug delivery and a passive or "grounding" electrode affixed to a second site on the skin to
enhance the rate of penetration of the medicament into the skin adjacent to the applicator electrode.

Recent interest in the use of iontophoresis for the transdermal delivery of drugs to a desired cutaneous or subcutaneous treatment site has stimulated a redesign of many of such drugs with concomitant increased efficacy of the drugs when delivered transdermally. As iontophoretic delivery of medicaments become more widely used, the opportunity for a consumer/patient to iontophoretically self-administer a transdermal dosage of medicaments simply and safely at non-medical or non-professional facilities would be desirable and practical. Similarly, when a consumer/patient travels, it would be desirable to have a personal, easily transportable apparatus available which is operable for the iontophoretic transdermal delivery of a medication packaged in a single dosage applicator. A problem which presents an impediment to potential users is the necessity for reformulating medicaments for iontophoretic delivery. Such reformulations must be approved by cognizant regulatory agencies prior to sale. This requires delay and additional expense for the manufacturer, which additional expense may be passed along to consumers. The present invention provides a disposable medicament dispensing electrode for use with a portable iontophoretic medicament delivery apparatus in which the electrode is adapted for use with the

apparatus for self-administering medicament. The medicament dispensing portion of the electrode can accept, store and dispense presently approved medicament formulations.

SUMMARY OF THE INVENTION

The present invention discloses a unit dosage medicament applicator electrode adapted for use with a portable iontophoretic transdermal or transmucoscal medicament delivery apparatus for the self-administration of a unit dose of a medicament into the skin. The electrode and current supply apparatus is particularly suited for the localized treatment of herpes infections. The established treatment for recurrent genital herpetic lesions has been primarily supportive; including local topical application of anesthesia. Severe cases have been treated with systemic Acyclovir®, Zovirax® (Glaxo-Wellcome) or Famvir® (SmithKline Beecham). Some cases the condition is managed with prophylactic long-term dosing administration with a suitable antiviral agent at great expense. Systemic treatment of acute herpetic flare-ups may reduce the normal 10-12 day course of cutaneous symptoms into a 6-8 day episode. Topical treatment of lesions with Acyclovir® has not been as effective as in vitro studies would suggest. A compound which is not presently available to clinicians but has demonstrated significant anti herpetic activity is 5-iodo-2 deoxyuridine (IUDR). Both of those agents have shown limited clinical efficacy when applied topically to the herpetic lesion. it is the present inventor's contention that the limited efficacy of topical administration previously observed is, at least in part, due to the poor skin penetration of these medicaments when applied topically. The present invention discloses a mesh-like iontophoresis electrode, which contains and dispenses pre-approved formulations of those medicaments and provides improved transdermal delivery of these medicaments.

Genital herpes (usually herpes simplex II infection) afflicts many people, cause

discomfort, shame, and may contribute to more severe and costly illnesses such as cervical cancer, prostate cancer, and perinatal blindness from herpetic conjunctivitis. Certain formulations containing anti-viral and/or anti-microbial drugs have been approved for topical application by the cognizant regulatory agency. Reformulation of such compositions for iontophoretic transdermal drug delivery entails significant delays before such technology is available to the public for general use. The present invention discloses a medicated iontophoresis electrode for the portable transdermal delivery of Acyclovir® (9-[(2-hydroxyethoxy)methyl]guanine) or similar anti-viral agent formulations which have already received (or may in the future receive) regulatory approval to greatly benefit these afflicted patients. In a second preferred embodiment of the invention, the medicament delivery electrode is attached to a user-wearable glove having one or more fingers or merely a finger cot covering at least a portion of one or more fingers of a user's hand.

It is an object of the present invention to provide an iontophoretic medicament delivery electrode which is adapted to be used with an iontophoresis device operable for self-administration of medicament into the skin of a person.

It is another object of the present invention to provide an improved iontophoretic transdermal drug delivery apparatus having a medicament-containing application electrode which disperses a single dosage and is disposable and non-reusable.

It is a further object of the present invention to provide an iontophoresis electrode meeting the above objectives which can receive and retain a previously approved drug formulation for dispensation by ionosonic transdermal delivery. It is still another advantage of the present invention to provide an improved disposable iontophoretic medicament applicator which meets the above objectives and which is inexpensive, safe to use and greatly increases the therapeutic

efficacy of a medicament administered thereby.

The medicament-containing electrode in accordance with the present invention, together with an iontophoresis apparatus, provides a means for transdermally administering medicament dispersed in a variety of previously approved formulations directly and with high efficiency into a diseased tissue thereby providing a novel method for treating clinical conditions presenting mucocutaneous symptoms and particularly mucocutaneous Herpes Simplex viral eruptions and sequelle associated therewith.

The above objects, features and advantages of the invention are realized by the improved monopolar iontophoretic medicament applicator electrode. The objects, features and advantages of the invention will become apparent upon consideration of the following detailed disclosure of the invention, especially when it is taken in conjunction with the accompanying drawings wherein:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a top plan view of a first embodiment of the disposable iontophoretic medicament delivery electrode for attachment to an iontophoresis handpiece wherein the medicament dispensing portion of the electrode is an open mesh;

FIG. 2 is a side elevational view of a preferred embodiment of the disposable non-reusable iontophoretic application electrode for use with an iontophoresis handpiece adapted for self-administration; and

FIG. 3 is a top plan view of the iontophoresis electrode in accordance with claim 2.

FIG. 4 is a horizontal cross-sectional plan view of an iontophoresis handpiece adapted for use with the embodiments of the medicament dispensing electrode of the present invention shown in Figures 1 .3.

FIG. 5 is a perspective view showing the applicator electrode of Figures 1 - 3 releasably affixed to the iontophoresis handpiece of Figure **4.**

FIG. 6 shows a patient preparing to self-administer medicament to a treatment site.

FIG. 7 is a top plan view of an embodiment of a medicament dispensing applicator electrode having unitary construction and an open mesh medicament dispensing portion similar to the embodiment shown in Figures 1 - 3 and adapted for attachment to the skin of a patient.

FIG. 8 is a horizontal cross-sectional view of the applicator electrode of Figure 7 taken along section line 8-8.

FIG. 9 is a bottom plan view of the applicator electrode of Figure 7.

FIG. 10 is a perspective view of an embodiment of an iontophoresis device and a medicament dispensing applicator electrode adapted to be releasably affixed to a finger of a patient wherein the medicament dispensing portion of the electrode is an open mesh.

FIG. 11 is a perspective view of the iontophoresis device and applicator electrode of Figure 10 wherein the applicator electrode has been removed from the patient's finger.

FIG. 12 is a partially cut-away view of the iontophoresis applicator electrode of Figures 10 and 11 showing the relationship between the applicator electrode, an insulating finger cot and a wrist-worn adaptation of the iontophoresis device shown in Fig. 4.

FIG. 13 is a plan view of a glove embodiment of the present invention having a large area electrode.

FIG. 14 is a perspective view of a patient using the glove embodiment of FIG. 13 to self-administer a medicament to a relatively large portion of skin underlying the glove, as in, for example, the treatment of acne.

DESCRIPTION OF THE PREFERRED EMBODIMENT

FIG. 1 shows, in top plan view, a first preferred embodiment of the hand-held iontophoretic transdermal medicament delivery apparatus of the present invention. The first preferred embodiment of the iontophoretic medicament-containing application electrode is shown at 10. The application electrode 10 is preferably disposable and non-reusable. The electrode 10 is suitable, for example, for transdermally delivering anti-viral agents such as Acyclovir® for the treatment of cold sores or genital herpes. The applicator electrode 10 is adapted for use with an iontophoresis handpiece such as the handpiece shown in Figures 4 and 5. In use, the applicator electrode 10 is detachably affixed to a hand-held iontophoresis handpiece 40 which handpiece presents a first electrically conductive surface 41 and a second electrically conductive surface 42. The handpiece 40 comprises a current driver *45* which receives an electrical voltage from a voltage multiplier 46 which is in electrical communication with one electrode 47 of an electrical power source 48 such as a battery. The other electrode 49 of the battery is in electrical communication with a tactile electrode 42 on the surface of the handpiece 40 which electrode is, in use, in contact with the skin of one or more fingers of a user. The electrical current from the current driver 45 is conducted through a wire or conductive strip 44 to the first electrically conductive surface 4 1. When the applicator electrode 10 is attached to the handpiece 40, the current passes through the conductive applicator electrode to the skin of the user, returning to the second electrically conductive element 42, or "tactile electrode" to drive the medicament 23 through the mesh-like matrix material 12 and into the user's skin. The medicament or treatment agent is contained within a viscous fluid vehicle which, in turn, is contained within a plurality of cellular apertures 12a comprising the mesh 12.

The applicator electrode 10 comprises a substantially flat elongate strip having lateral ends extending from a central portion. The central medicament dispensing portion 12 is of mesh-like construction and has vertical cells dimensioned to accommodate a viscous fluid within the confines of the cellular structures. The viscous fluid contained within each of the plurality of cells 12a includes a medicament (not shown) which is in a form suitable for transport under the influence of an electrical current. The lateral ends of the applicator electrode 10 include a mesh-like tactile conductive portion 11 which contains an electrically conductive gel therewithin. The applicator electrode 10 has an upper skin-facing surface 13 and a lower, device-facing surface 14. One or a plurality of cells 12a form one or a plurality of apertures between the upper skin-facing surface 13 and the lower device-facing surface 14. The device-facing surface 14 may further include an adhesive layer 18 applied thereto suitable for releasably adhering the applicator electrode 10 to the positive (anode) or negative (cathode) pole of a iontophoresis handpiece. The positioning of the electrode's tactile conductive portion 11 on the surface of the handpiece is such that tactile conductive portion 11 makes electrical contact with the tactile electrode 42 on the handpiece. When the applicator electrode 10 is correctly positioned on the handpiece, the medicament dispensing reservoir 12 is in electrical communication with the electrically contacting element 41 on the handpiece. In addition, one or more small magnets 15 may positioned on the handpiece to activate a switch within said handpiece which turns the handpiece on and/or off. The relatively narrow, flexible areas 16 on the electrode enable the applicator electrode 10 to be bent and formed around the handpiece. Figure 2 shows a cross-sectional view of the applicator electrode 10 of Figure 1 taken along section lines 2-2. The material 17 forming the structural portion of the applicator electrode 10 is preferably a non-electrically conducting elastomer. A

bottom view of the applicator electrode 10 of Figures 1 and 2 is shown in Figure 3.

Figure 5 is a perspective view of the applicator electrode 10 attached to the handpiece 40 in position for use. Figure 6 shows a patient preparing to use the iontophoresis device for administering medicament to herpes lesions on the face. The patient 60 grasps the tactile electrode 42 with a finger 61 to make electrical communication therewith. The patient then touches the tip 1 2 of the applicator electrode 1 0 to the lesion 63 thereby completing the electrical circuit and the resulting current flow driving the medicament into the skin.

Turning next to Figure 7, a second preferred embodiment of a medicament dispensing applicator electrode in accordance with the present invention is shown at 70. The centrally located medicament dispensing portion 71 has cells 72 therewithin which cells provide an aperture between the upper surface 73 and the lower, skin-contacting surface 74 of the electrode 70. The applicator electrode 70 is shown in cross-section along section lines 8-8 in Figure 8. The central medicament dispensing portion 71 of the electrode 70 is mesh-like in construction. A plurality of vertical cells 72 are molded within the elastomer strip comprising the applicator electrode to form apertures which communicate between the upper surface 73 and the lower surface 74. A fluid or semi-fluidic vehicle containing a medicament is placed within the cells 72 which cells are dimensioned to retain the medicament therewithin until an electrical current is passed therethrough. An adhesive layer 75 is coated upon the lower surface 74 of the applicator electrode. The adhesive is chosen to be hypoallergenic, biocompatible and to releasably affix the electrode 70 to the skin.

A bottom view of the applicator electrode of Figures 7 and 8 is shown in Figure 9. In use, the embodiment of the applicator electrode 70 shown in Figures 7-9 is affixed to the skin via the

adhesive surface 75. The iontophoresis handpiece 40 is grasped between the fingers of the patient such that the tactile electrode (42 in Fig. 5) is in contact with at least one of the patient's fingers. The handpiece is then advanced to the medicament dispensing portion 71 of the applicator electrode 70 until it makes contact therewith. The circuit formed between the fingers grasping the tactile electrode 42 portion of the handpiece 40 and the lesion is made through the mesh surface of the medicament dispensing portion of the applicator electrode. Current flows through the handpiece to the medicament dispensing electrode and into the skin of the patient to return to the handpiece via the fingers and the tactile electrode to close the circuit. As the current flows through the medicament dispensing electrode the current drives the medicament into the skin of the patient.

Turning now to Figure 10, a thimble-like medicament dispensing applicator electrode 100 is shown attached to a finger 105 of a patient. The applicator electrode 100 is in electrical communication with one pole (cathode or anode) of a wrist-worn, bipolar iontophoresis device 101 by means of a wire 102. The bottom 106 or wrist-facing, skin-contacting surface of the bipolar iontophoresis device 101 is the other pole (anode or cathode) comprising a conductive electrode. The iontophoresis device 101 is releasably affixed to the wrist by means of a strap 103. The iontophoresis device 101 may be constructed similarly to the iontophoresis handpiece 40 except that the working electrode ~~41~~ 112 is attached to the wire 102 and the tactile electrode 42 replaced with a conductive electrode 106 forming the skin-contacting portion of the device 101 which is in contact with the wrist of the patient. The applicator electrode 100 is electrically isolated from the finger 105 by means of an insulating finger cot 104. Current from the iontophoresis device 101 passes through the conductive wire 102 to an inner electrically

conductive thimble 110 (Figure 11) to which the wire is conductively attached by means of solder. The electrically conductive thimble 110 has an overlying silicone elastomeric thimble 111. The elastomeric thimble 111 is homogenous in composition and has an upper surface 112 and a lower surface 113 which comprises a mesh 113a. The mesh 113a has integral therewith a plurality of retaining cells 114 which cells extend between the electrically conductive thimble 110 and the lower surface 113 and are dimensioned to contain a medicament. In operation, current from the iontophoresis device 101 passes through the wire 102 to the electrically conductive thimble 110 of the applicator electrode. The voltage applied to the surface of the electrically conductive thimble 110 drives medicament contained within the cells 114 of the mesh 113 into the skin of a user's body. The current passes through the user's body to the conductive electrode (not shown) which comprises the wrist-facing portion of the iontophoresis device 101. The iontophoresis device 101 preferably includes a power source, a voltage multiplier, a driver and an on/off switch as shown in the handpiece 40, but reconfigured to be worn on the wrist. An enlarged perspective view of the applicator electrode 100 overlying a finger cot is shown in structural relationship in Figure 12.

The simple design is capable of retaining and dispensing existing medicament formulations and the size of the retaining cells 72 in the mesh portion of the electrode may be varied. The structural matrix of the applicator electrode is a flexible hypoallergenic, non-electrically-conductive material. A suitable material is Silastic®, a silicone elastomer which is biocompatible, non-conductive, flexible and possessing sufficient structural rigidity to contain medicaments and a delivery vehicle within the retaining cells 114. Further, Silastic silicone elastomer is inert so that medicaments will not oxidize or otherwise have their chemical structures damaged. An electrode constructed from silicone elastomer has a prolonged shelf-life, is soft and

pleasant on contact, is hypoallergenic and sufficiently flexible to adhere to any anatomical contour such as presented by a thimble. Such anatomical plasticity is a key advantage to the foregoing design. Other polymers, such as polyurethane, are suitable as well. A hydrated hydrophilic cotton layer (not shown) may be interposed between the medicament dispensing portion 71 and the electrically conductive surface 4 1 of the handpiece 40 to provide pretreatment hydration of the medicament dispensing portion or the mesh may be hydrated by the patient immediately prior to use.

With reference to the embodiment of an iontophoresis applicator electrode shown in Figures 7-9, the electrode is easily manufactured using mold technology wherein uncured silicone elastomer is either poured into a complementary mold or pressure-mold injected. The lower surface 74 of the non-medicament dispensing portion of the electrode is coated with skin adhesive. The medicament dispensing portion 71 functions as a medicament reservoir and is preferably between 1 mm and 4mm thick, depending upon the amount of medicament required to be stored in the cells 72. The medicament-retaining cells 72, which are preferably a hexagonal, honey comb-like structure, retain the medicament therein through their surface tension. Hexagonal cells also lessen cross channel conductivity by means of their vertical orientation. The size and geometry of these cells can vary. The smallest cells, for instance, would be more suited to retaining liquid medicaments while the larger cells are better adapted to retain ointment-based medicaments. Medium cells are more suited to retaining and dispensing gel medicaments and lotions. The silicone walls of the cells can be chemically modified to change the hydrophobic surface characteristics thereof and further improve retention of specially formulated liquid medicaments. For additional cell stability and retention capabilities, the skin-facing surface of the cells can be

covered with non-wicking, fibrous and porous materials commonly used in electrodes. A composite or unitary construction from a single mold can be used depending on production cost, it is inexpensive to manufacture and it offers both a compartment for storage of existing formulations as well as a structural backbone for the application electrode. The surface treatments of the retaining material bounding each of the cells to create hydrophilic or hydrophobic surface effects depending on the formulation to be utilized is well known in the art. An example of such technology is disclosed, for example, in US patent *5,589,563.* For ointments and hydrophobic materials, silicone is preferred. For water or gel medicaments, surface treatment such as doping the elastomeric cell surface with hydrophilic molecules can be of additional benefit, as described herein. The embodiments disclosed herein present the following advantages:

Inexpensive manufacture;

Use of either injection or pour molding production;

Use of composite sheet cutout assembly;

Anatomically conforming;

Elastomer surface modification for optimum retention of medicament;

Variable retaining cell size;

Variable retaining cell geometry;

Ability to utilize existing medicament formulations;

May use a cotton or (other hydrophilic matrix) layer for rapid pre-treatment hydration.

May be used with single or multi-channel dispersive iontophoretic drivers; and

May be used with iontophoretic or ionosonic devices.

An embodiment of the present invention adapted for delivering medicament to a large area

of skin is shown in Figure 13. The iontophoresis electrode is contained within a glove adapted to conform to and be worn upon a patient's hand. The glove embodiment 130 of the iontophoresis drug delivery electrode comprises an elastomeric glove 13 1 having a plurality of holes or open pores 132 in the palmar surface 133 thereof Underlying the palmar surface 133 and disposed within the glove between the skin 134 and glove is an electrically insulating sheet 135 having an inner surface 136 and an outer surface 137, both of which surfaces are coated with an electrically conductive layer 138. The inner conductive layer 136 is, in use, in electrical communication with the skin. The outer conductive layer 137 is in contact with the interior surface of the glove and the pores 132. A medicament 139 capable of iontophoretic transdermal delivery is contained within the pores. A bipolar power source 140 has a working electrode 141 in electrical communication with the outer conductive layer 137 coating the electrically insulating sheet 135, and a ground electrode (not shown) which is in electrical communication with the inner conductive layer coating the electrically insulating sheet. When the power source 140 is energized, an electrical current flows between the inner conductive layer and the outer conductive layer, which layers are separated by the electrically insulating sheet, via the patient's skin. The polarity and amplitude of the current flowing through pores into the user's skin facilitates entry of the medicament into the skin. The glove embodiment, shown in use in Figure 14, is particularly useful for transdermally delivering medicament to large areas of skin.

The advantages of a unitary iontophoresis electrode and a glove and finger cot embodiment of an iontophoresis electrode for drug delivery have been presented. It is noted that similarly constructed electrodes may be employed for non-invasively collecting molecular species from the blood. For example, the mesh may be impregnated with an electrically conductive gel.

The polarity of the gel, with respect to the skin, may be employed to transport blood components through the skin into the gel where such components may be detected and/or quantitated. Such measurements are useful for monitoring blood levels of compounds such as glucose or drugs.

While the invention has been described above with references to specific embodiments thereof, it is apparent that many changes, modifications and variations in the materials, arrangements of parts and steps can be made without departing from the inventive concept disclosed herein. For example, an impregnated conductive gel can also be used to as medicament containing medium to increase the physical stability and the tissue adhering characteristics of the electrode. Accordingly, the spirit and broad scope of the appended claims is intended to embrace all such changes, modifications and variations that may occur to one of skill in the art upon a reading of the disclosure. All patent applications, patents and other publication cited herein are incorporated by reference in their entirety.

What I claim is: